36. (Twice amended) A pharmaceutical composition comprising in an amount effective for the treatment or prevention of cancer or an immune disorder, or for activating or augmenting an immune response: (a) a molecule that binds CD40, which molecule increases the binding of CD40 ligand to cell surface CD40 on B cells by at least 45%; (b) CD40 ligand; and (c) a pharmaceutically acceptable carrier.

REMARKS

Claims 1-9, 21-25, 34-36, 38, 39, 42-44 and 47-91 are pending in the instant application.

Claim 36 has been amended to clarify that which Applicants regard as the invention. The amendment to claim 36 is fully supported by the specification, for example at page 13, lines 6-7 and page 54, lines 6-17. No new matter is added.

INTERVIEW SUMMARY RECORD

Applicants and Applicants' representatives thank Supervisory Patent Examiner Anthony Caputa and Examiner Karen Canella for the courtesy of the recent interview in connection with the above-identified application. Pursuant to 37 C.F.R. § 1.133 and M.P.E.P. 713.04, Applicants present this interview Summary Record of the interview of September 24, 2002 ("the Interview") between Supervisory Patent Examiner Anthony Caputa and Examiner Karen Canella, Applicant Dr. H. Perry Fell, and Applicants' representatives, Adriane M. Antler and Muna Abu-Shaar, in connection with the above-referenced application. During the Interview, the outstanding Office Action was discussed.

Applicants' representative, Attorney Adriane M. Antler, presented arguments as to why the amendment to claims 21, 22, 23, 24, 47, 48, 51, 52, and 69, made in the Amendment of February 28, 2002, did not introduce new matter. Supervisory Patent Examiner Caputa and Examiner Canella agreed that the amended claims were supported by the specification.

Applicant and Applicants' representative also presented arguments as to why the instantly claimed invention was not made obvious by the prior art relied upon by Examiner Canella in the instant Office Action. Supervisory Patent Examiner Anthony Caputa and Examiner Karen Canella agreed that the obviousness rejections would be

overcome as long as the claims recited structural (*i.e.*, either the S2C6 heavy chain CDR or variable region sequences or closely related sequences) or functional characteristics (*i.e.*, increasing the binding of CD40 ligand to cell surface CD40 on B cells) that distinguished the claimed antibodies and pharmaceutical compositions comprising them from the prior art antibodies.

Details of these arguments are presented below.

THE OBJECTION UNDER 35 U.S.C. § 132 SHOULD BE WITHDRAWN

The Amendment of February 28, 2002 is objected to, because the amendments made to claims 21, 22, 23, 24, 47, 48, 51, 52, and 69 allegedly introduce new matter. According to the Examiner, the foregoing claims "have been amended to read on increasing the binding of CD40 ligand to the cell surface CD40 on B cells 'by at least 45%'" whereas the specification states at page 54, lines 15-18 that "the increase in CD40 ligand binding afforded by the S2C6 antibody complexed to Ramos B cell surface CD40 was 51% to 68%." The Examiner concludes that the amendment lacks sufficient support. Applicants disagree for the reasons discussed below.

The Examiner's punctuation indicates that the recitation of "by at least 45%" was the amendment made by Applicants to claims 21, 22, 23, 24, 47, 48, 51, 52, and 69. However, the amendment made to those claims was the inclusion that the antibody increase the binding of CD40 ligand to cell surface CD40 on B cells. Applicants noted the proper support in the specification for this claim language, namely at page 54, lines 6-8 of the specification. Thus, the language of the claim amendment is fully supported by the specification as filed.

Applicants further submit that not only was the language of the claim amendment supported in the specification, the claim as a whole was contemplated by the specification. In particular, the Examiner's attention is directed to page 12, line 23 through page 13, line 7 of the specification, which describes generally the molecules of the invention, and to page 13, lines 6-7, which clearly identifies molecules of the invention as encompassing those anti-CD40 antibodies that bind to CD40 and increase the binding of CD40 ligand to CD40 by at least 45%, 50%, 60% or 65%. Further, the specification at pages 53, lines 16-18 and 54, lines 6-8, respectively, demonstrates that this increase in

binding is contemplated in the context of CD40 ligand binding to cell surface CD40 on B cells.

In view of the foregoing, Applicants submit that the objection to the claim amendments of February 28, 2002 have been obviated and should be withdrawn, as agreed during the Interview.

THE REJECTIONS UNDER 35 U.S.C. § 103 SHOULD BE WITHDRAWN

All pending claims are rejected under 35 U.S.C. § 103 as obvious over four different combinations of references.

The Law of Obviousness

To establish a *prima facie* case of obviousness, the teachings of the prior art must provide one of ordinary skill in the art with some suggestion or motivation to make the claimed composition. *In re Rijckaert*, 28 U.S.P.Q.2d 1955, 1956 (Fed. Cir. 1993). For a claimed invention to be deemed obvious in view of a prior art disclosure, the prior art disclosure must, firstly, give rise to a *suggestion of or motivation for* the claimed subject matter. Assuming such a suggestion or motivation is found, and the invention is thus arguably "obvious to try" to achieve, only then does one reaches the question of whether one of ordinary skill in the art would have had a reasonable expectation of success in achieving it. *See e.g.*, *In re Vaeck*, 947 F.2d 488, 493 (Fed. Cir. 1991); *In re Dow Chemical Co.*, 837 F.2d 469, 473 (Fed. Cir. 1988). Both the suggestion of the claimed invention and the expectation of success must be in the prior art, not in the disclosure of the claimed invention. *In re Dow Chemical Co.*, 837 F.2d 469 (Fed. Cir 1988).

"Measuring a claimed invention against the standard established by section 103 requires the oft-difficult but critical step of casting the mind back to the time of invention, to consider the thinking of one of ordinary skill in the art, guided only by the prior art references and the then-accepted wisdom in the field." *In re Dembiczak*, 175 F.3d 994, 999 (Fed. Cir.1999), abrogated on other grounds, citing to *W.L. Gore & Assoc., Inc. v. Garlock, Inc.*, 721 F.2d 1540, 1553 (Fed. Cir. 1983). In particular, the Examiner cannot use hindsight reconstruction to pick and choose among isolated disclosures in the prior art to

deprecate the claimed invention. *In re Fine*, 837 F.2d 1071, 1075 (Fed. Cir. 1988). Care must be taken to avoid hindsight reconstruction by using Applicants' disclosure "as a guide through the maze of prior art references, combining the right references in the right way so as to achieve the result" of the claims in question. *Grain Processing Corporation v. American Maize-Products Company*, 840 F.2d 902, 907 (Fed.Cir.1988), citing *Orthopedic Equip. Co. v. United States*, 702 F.2d 1005, 1012 (Fed.Cir.1983).

Applicants submit that, the Examiner, in raising the obviousness rejections, is employing, perhaps unconsciously, a hindsight reconstruction without casting her mind to the state of the art at the time of filing the present application. As stated above, such hindsight reconstruction does not meet the legal standard for obviousness. Each of the combinations cited by the Examiner is discussed in turn below to demonstrate that, standing in the shoes of the Applicants at the time the present application was filed, there was no suggestion of or motivation in the art to practice the claimed invention.

I. The Rejection of Claims 36 and 61 over Hirano in View of Pound Should Be Withdrawn

Claims 36 and 61 are rejected under 35 U.S.C. § 103(a), allegedly as being unpatentable over Hirano *et al.*, 1999, Blood 9:2999-3007 ("Hirano") in view of Pound *et al.*, 1999, International Immunology 11:11-20 ("Pound"). According to the Examiner, Hirano teaches the inhibition of "human breast carcinoma cells by a soluble CD40 ligand" and that "preliminary data indicated that ovarian carcinomas and bladder carcinomas are also inhibited in vitro by the CD40 ligand, suggesting that CD40 stimulation may be beneficial in the treatment of these tumors in vivo." The Examiner further states that Hirano suggests "a composition comprising an anti-CD40 monoclonal antibody and CD40 ligand, wherein the anti-CD40 antibody is not an antagonist of the CD40 receptor in order to assess synergism between the CD40 ligand and the anti-CD40 antibody." With respect to Pound, the Examiner states that Pound teaches "the monoclonal antibody of 5C3 which increases the binding of the CD40 ligand to the CD40 receptor on T-cells." The Examiner states that it is "reasonable to conclude that 5C3 antibody would increase the binding of the CD40 ligand to the B cell receptor as the CD40 receptor does not differ in structure when expressed on B cells versus T cells." The Examiner concludes that it would have been

prima facie obvious for one of skill in the art to combine the teachings of Hirano and Pound to arrive at the invention claimed in claims 36 and 61. Applicants respectfully disagree for the reasons discussed below.

First, Applicants note that claim 36 as amended herein, and therefore claim 61 dependent thereon, recites a pharmaceutical comprising a molecule that binds CD40, which molecule increases the binding of CD40 ligand to cell surface CD40 on B cells by at least 45%, and CD40 ligand.

With respect to Hirano, while Hirano teaches that CD40 ligand inhibits the growth of breast cancer cells, Hirano does not teach that an anti-CD40 antibody having the characteristics of S2C6, *i.e.*, the ability to increase the binding of cell surface CD40 on B cells to CD40 ligand, can be useful to treat cancer. In particular, Hirano, while promoting the advantages of soluble CD40 ligand over monoclonal antibodies (Hirano at 3006, left column, third paragraph), states that "anti-CD40 MoAbs [other than M3] *may* be able to exert growth-inhibitory effects on carcinoma cells. It may also be of interest to combine the ligand with anti-CD40 MoAbs to assess potential synergistic effects" (Hirano at 3006, left column, first paragraph) (emphasis added). A general invitation to experiment without specific teachings on how to achieve the desired result does not raise a *prima facie* case of obviousness. *Hybritech Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d 1367, 1380 (Fed. Cir. 1986). At best, Hirano provides an invitation to experiment combining CD40 ligand with non-antagonist CD40 antibodies. As discussed above, Hirano does not teach that an anti-CD40 antibody having the characteristics of S2C6, *i.e.*, the ability to increase the binding of cell surface CD40 on B cells to CD40 ligand, alone or in combination with CD40 ligand, can be useful in a pharmaceutical composition. Nor does Hirano teach that S2C6 has such ability. Accordingly, in view of the applicable case law, Hirano does not render obvious the presently claimed invention of claims 36 and 61.

Pound does not remedy the deficiencies of Hirano. In particular, Pound does not teach, suggest, provide motivation for, producing a pharmaceutical composition comprising a molecule that increases the binding of CD40 ligand to cell surface CD40 on B cells by at least 45% and CD40 ligand. Pound compares various characteristics of eight different anti-CD40 monoclonal antibodies, including S2C6. Pound describes cross-blocking experiments among the antibodies, the antibodies' ability to block binding of

soluble CD40 to cell surface CD40 ligand on T cells, and rescue of B cells from apoptosis, and in the discussion focuses on mechanisms of CD40 receptor signaling. Nowhere does Pound suggest or provide motivation for using any of the antibodies in pharmaceutical compositions, alone or with CD40 ligand. Pound, accordingly, does not render obvious the invention presently claimed in claim 36 and 61.

The Examiner believes that Hirano suggests using an antibody such as 5C3, as described by Pound, in pharmaceutical compositions that further comprise CD40 ligand. Applicants have discussed why the suggestion of Hirano is no more than an invitation to experiment using combinations of CD40 antibody and CD40 ligand. However, even assuming *arguendo* that the combination of Hirano and Pound suggested a composition comprising CD40 ligand and the anti-CD40 antibody 5C3, a conclusion that the presently claimed invention is obvious still cannot be reached. As Applicants pointed out to the Examiners during the interviews of February 7, 2002 and September 24, 2002, the experiments of Pound show that 5C3 is clearly distinct from the S2C6-like anti-CD40 molecules present in the compositions of claims 36 and 61. Specifically, Pound demonstrates that the binding activities of S2C6 and 5C3 are dramatically distinct when compared side by side.

In particular, the Examiner's attention is directed to Table 1 of Pound, which compares the effects of various antibodies on the binding of CD40 ligand on the surface of T cells to a soluble CD40-immunoglobulin fusion protein ("CD40-Fc") (NOT to cell surface CD40 on B cells), and the inhibitory effects of the eight anti-CD40 antibodies in the employed in the Pound experiments on the binding of S2C6 to cell surface CD40. Where the effect of the various antibodies on the binding of CD40 ligand to soluble CD40-Fc was examined, the CD40-Fc was preincubated with the test antibody, and the ability of the test antibody-CD40-Fc complex to bind to CD40 ligand on activated T cells was measured relative to CD40-Fc preincubated with a control antibody (see section entitled "Inhibition of binding of soluble CD40 to CD40L on T cells" at page 12, right hand column). Where the effect of the various antibodies on the binding of S2C6 to cell surface was examined, resting B cells were preincubated with the test antibody, after which time the cells were incubated with S2C6. The ability of the pre-bound test antibody to inhibit S2C6 binding to the resting

B cells was measured (see section entitled "Inhibition of binding of CD40 mAb S2C6 to CD40 on B cells" at page 13, left hand column).

Under these experimental conditions, S2C6 decreased CD40-Fc binding to CD40 ligand on T cells by approximately 82%, whereas 5C3 increased CD40-Fc binding to CD40 ligand on T cells by approximately 32% (Table 1, first line of data). These data provide conclusive evidence that S2C6 and 5C3 have different epitope specificities, and therefore could not share the same or closely related set of heavy chain CDRs. Furthermore, binding of 5C3 to B cells did not preclude to a significant degree (22%) the subsequent binding of S2C6 to cell surface CD40 (Table 1, second line of data), indicating that CD40 can simultaneously bind to S2C6 and 5C3. This provides yet further evidence that the two antibodies are distinct both functionally and structurally. The sum of the data presented in Pound demonstrates, as depicted in Figure 7 of Pound, distinct epitope specificities of S2C6 and 5C3. Accordingly, even if one could glean from Hirano and Pound together a suggestion to use 5C3 in a pharmaceutical composition with CD40 ligand, the clearly different characteristics of S2C6 described in Pound would teach away from using S2C6-like antibodies in pharmaceutical compositions with CD40 ligand.

In view of the foregoing, Applicants submit that the rejection of claims 36 and 61 under 35 U.S.C. § 103 has been obviated and should be withdrawn.

II. The Rejection of Claims 36, 61, and 69-71 over Hirano and Pound in view of de Boer Should Be Withdrawn

Claims 36, 61, and 69-71 are rejected under 35 U.S.C. § 103(a), allegedly as obvious over Hirano and Pound in view of U.S. Patent No. 5,874,082 to de Boer ("de Boer"). According to the Examiner, Pound teaches the 5C3 antibody which "increases the binding of CD40 ligand to the CD40 receptor on T or B cells," and Hirano teaches the motivation for administering said antibody to treat breast, ovarian, and bladder carcinomas." The Examiner further states that de Boer teaches humanized forms of the anti-CD40 antibodies 5D12, 3A8, and 3C6, rendering it *prima facie* obvious for one of skill in the art to "humanize the 5C3 antibody for administration to humans," thereby rendering obvious claims 36, 61, and 69-71.

First, Applicants again note that claim 36 as amended herein, and therefore claims 61 and 69-71 dependent thereon, recite a pharmaceutical comprising a molecule that binds CD40, which molecule increases the binding of CD40 ligand to cell surface CD40 on B cells by at least 45%, and CD40 ligand.

Further, as discussed above, Applicants submit that the suggestion of Hirano which, when read in the context of the entire reference, merely presents an invitation to experiment by combining non-antagonistic anti-CD40 antibodies with CD40 ligand. As further noted above, Pound fails to remedy the deficiencies of Hirano, as Pound does not suggest or provide motivation for use of anti-CD40 antibodies that increase the binding of CD40 ligand to cell surface CD40 on B cells, alone or in combination with CD40 ligand, in pharmaceutical compositions, let alone such antibodies that increase the binding of CD40 ligand to cell surface CD40 on B cells by at least 45%. Neither reference suggests the therapeutic use of S2C6-like molecules.

de Boer does not remedy the deficiencies of Hirano or Pound. de Boer describes the anti-CD40 antibodies 5D12, 3A8, and 3C6, a class of antibodies which prevents the growth and differentiation of B cells and *blocks* the CD40-CD40L interactions (see, *e.g.*, *de Boer* at Column 12, line 67 through column 13, line 1, characterizing the de Boer antibodies as "blocking the CD40-CD40 ligand interaction"), in direct contrast to the functional limitation recited in claim 36. This blocking activity of the de Boer antibodies is clearly in the context of cell surface CD40 on B cells, as the blocking assays of de Boer measured the inhibition of T-cell-induced B-cell proliferation (*de Boer* Example 5, columns 18-19). The teachings of de Boer of humanizing 5D12 and suggesting the humanization of 3A8 and 3C6 are based on the inhibitory property of these antibodies, which is stated to make these antibodies useful to treat disorders characterized by overproduction of antibodies, such as autoimmune disorders. *de Boer* at column 3, lines 6-8 and 52-54. Accordingly, de Boer does not remedy the deficiencies of Pound or Hirano, as de Boer does not suggest or provide motivation for humanization of antibodies that promote proliferation of normal B cells, such as antibodies that increase the binding of CD40 ligand to cell surface CD40 on B cells, let alone pharmaceutical compositions comprising such antibodies and CD40 ligand.

In view of the foregoing, Applicants submit that the rejection of claims 36, 61, and 69-71 under 35 U.S.C. § 103 is obviated and should be withdrawn.

III. The Rejection of Claims 4, 5, 38, 62, 80, 81, 83-85 and 89-91 over Francisco in view of Paulie Should Be Withdrawn

Claims 4, 5, 38, 62, 80, 81, 83-85 and 89-91 are rejected under 35 U.S.C. § 103(a), allegedly as obvious over Francisco *et al.*, 1997, J. Biol. Chem. 272(39):24165-9 ("Francisco") in view of Paulie *et al.*, 1989, J. Immunol. 142(2):590-5 ("Paulie"). The rejected claims are drawn to molecules comprising the sequences of the S2C6 heavy chain CDRs or variable region, or closely related sequences, fused to non-antibody sequences, for example a toxin sequence, and pharmaceutical compositions comprising such molecules. According to the Examiner, Francisco teaches single chain immunotoxins of the monoclonal anti-CD40 antibody G28-5 fused bryodin and pseudomonas exotoxin, respectively, to which certain carcinomas or B cell malignancies were sensitive. According to the Examiner, Paulie teaches that "S2C6 antibody binds at a proximal epitope to that bound by the G28-5 antibody" and that S2C6 and G28-5 bind similar cell types. The Examiner concludes that it would have been *prima facie* obvious for one of skill in the art to "substitute the variable heavy and light chains of the S2C6 antibody for the variable heavy and light chains of the G28-5 antibody" in the G28-5 immunotoxins," thereby rendering obvious claims 4, 5, 38, 62, 80, 81, 83-85 and 89-91. Applicants respectfully disagree, as discussed below.

Francisco teaches the production of a single chain immunotoxin, BD1-G28-5 sFv, comprising the heavy and light chain variable regions of the anti-CD40 antibody G28-5 and bryodin 1. The immunotoxin was found to bind to soluble CD40 and was cytotoxic to B cell malignancies (Francisco at page 24167, bottom left column and entire right column), cytotoxic to monocytes activated with IFN-γ (but not to non-activated monocytes) (Francisco at page 24168, top left column). The immunotoxin was found to be ineffective in killing carcinoma cells (Francisco at page 24168, bottom left column). In the discussion, Francisco compares and contrasts the activities of BD1-G28-5 sFv with the earlier-published G28-5-PE40 sFv, a G28-5 based immunotoxin comprising *Pseudomonas* exotoxin. BD1-G28-5 was comparable to G28-5-PE40 in all activities, with the exception

of a failure to exert a cytotoxic effect on carcinoma cells, in contrast to G28-5-PE40. Francisco's teaching are based on G28-5-based immunotoxins, and does not teach, suggest or provide any motivation for making S2C6-based immunotoxins.

Paulie does not remedy the deficiencies of Francisco. Paulie describes the requirements of B cell stimulation by anti-CD40 antibodies. Paulie also describes that S2C6 induces B cell proliferationa nd that both G28-5 ad S2C6 recognize CD40 on B lymphocytes, and can block binding of each other. Paulie describes ELISA experiments to characterize antibodies other than S2C6 suspected to bind to B cell antigens. Of these antibodies, G28-5 bound CD40. S2C6 and G28-5 displayed competitive inhibition of the binding of one another; however, G28-5 was more effective, leading Paulie to suggest that G28-5 has higher affinity to CD40 than does S2C6 (Paulie at page 592, right column). As would be expected of two anti-CD40 antibodies, similar staining profiles against a panel of cell lines were observed for the two antibodies. Nothing in the findings of Paulie suggests production of fusion proteins comprising sequences from S2C6. If anything, Paulie teaches against the use of S2C6 for therapeutic purposes, as it implies that S2C6 can promote the proliferation of cancer cells (*see* Paulie at page 594, bottom left column). Accordingly, Paulie, whether alone or in combination with Francisco, does not teach, suggest or provide motivation for cloning S2C6, let alone motivation for making molecules comprising the heavy chain CDR or variable regions of S2C6 fused to non-antibody molecules. To find otherwise, when none of the reference cited by the Examiner "convey or suggest that knowledge, is to fall victim to the insidious effect of a hindsight syndrome wherein that which only the inventor taught is used against its teacher." *W.L. Gore*, 721 F.2d at 1553.

As discussed above, neither Francisco nor Paulie provides any suggestion of a therapeutic use of S2C6-like molecules. Indeed, despite the allegations made by the Examiner that the prior art teaches that G28-5 and S2C6 are similar and that, accordingly, one of skill in the art would be motivated by the teachings of Francisco and Paulie to make recombinant molecules comprising the heavy chain CDR or variable regions of S2C6, the Examiner ignores (i) a lack of any suggestion by Francisco to make immunotoxins other than the G28-5-based immunotoxin taught therein; as well as the teachings of Paulie (ii) that G28-5 has a higher binding affinity to CD40 than S2C6 and (iii) that making recombinant molecules comprising the CD40 for the purpose of cancer therapy is likely

undesirable given Paulie's findings that CD40-expressing cancer cell lines can be made to "propagate in response to antibody treatment" without preactivating agents.

Applicants take this opportunity to point out that the very different properties of G28-5 and S2C6, which would also lead one of skill in the art away from cloning S2C6 on the basis of the teachings Francisco reference regarding G28-5-based immunotoxins. First, with respect to the ability to promote binding of CD40 ligand to CD40, Applicants note in the specification, in particular at page 54, lines 24-29, that "[t]hese data indicate that S2C6 differs surprisingly from G28-5... in its ability to increase CD40L/CD40 interaction." Further, not only does Applicants' specification teach that G28-5 and S2C6 differ greatly in the ability to promote the binding of CD40 ligand to CD40, but so does the art. In particular, Pound, discussed in Sections I and II above, teaches that S2C6 and G28-5 are vastly different with respect to their ability to promote B cell proliferation in the presence of soluble trimeric CD40 ligand (sCD40LT): S2C6 and sCD40LT have synergistic stimulatory effects on proliferation of resting B cells, whereas G28-5 has no evidence of such a cooperative interaction with sCD40LT. Pound also concludes that G28-5 and S2C6 have distinct epitope specificities (see Figure 7 of Pound).

In view of the foregoing, Applicants submit that the rejection of claims 4, 5, 38, 62, 80, 81, 83-85 and 89-91 as obvious over Francisco in view of Paulie is improper and should be withdrawn.

IV. The Rejection of Claims 1-9, 21-25, 34, 38, 39, 42-44 and 47-91 over Francisco, Paulie, Hirano, de Boer, Riechmann and Greenwood Should Be Withdrawn

Claims 1-9, 21-25, 34, 38, 39, 42-44 and 47-91 are rejected under 35 U.S.C. § 103(a), allegedly as obvious over Francisco and Paulie and further in view of Hirano, de Boer, Riechmann *et al.*, 1988, Nature 332:323-327 ("Riechmann") and Greenwood *et al.*, 1993, "Effector Functions of Matched Sets of Recombinant Human IgG Subclass Antibodies, In: Protein Engineering of Antibody Molecules for Prophylactic and Therapeutic Applications in Man," Mark Clark, Ed., pp. 85-100 (Greenwood).

The rejected claims are drawn to molecules comprising the sequences of the S2C6 heavy chain CDRs or variable region, or closely related sequences, fused to a heterologous molecule, such as a human immunoglobulin constant domain or non-antibody

molecule, molecules that compete for binding to CD40 with S2C6 and either comprise S2C6 CDR sequences or increase the binding of CD40 to cell surface CD40 ligand on B cells by at least 45%, molecules that increase the binding of CD40 to cell surface CD40 ligand on B cells by at least 45%, molecules having combinations of the foregoing characteristics, and pharmaceutical compositions comprising such molecules, optionally in combination with CD40 ligand.

According to the Examiner, the combination of Francisco and Paulie renders obvious a fusion protein comprising the variable regions of S2C6; Hirano suggests a composition comprising non-antagonistic CD40 antibodies and CD40 ligand; Riechman teaches the advantages of human immunoglobulin constant domains; Greenwood teaches constant domains of the IgG isotype; and de Boer teaches humanized forms of the anti-CD40 antibodies 5D12, 3A8 and 3C6. The Examiner concludes that it would have been *prima facie* obvious to arrive at the invention "as a whole" claimed in claims 1-9, 21-25, 34, 38, 39, 42-44 and 47-91. Applicants respectfully disagree.

As discussed above, to rise to the level of a *prima facie* case of obviousness, the teachings of the prior art must provide one of ordinary skill in the art with some suggestion or motivation to make the claimed composition. None of the references cited by the Examiner, alone or in combination, provide any suggestion or motivation of the therapeutic use of S2C6-like molecules, or to clone S2C6 and/or to make molecules comprising the heavy chain CDRs or the heavy chain variable region of S2C6 or related sequences. As discussed above, Francisco's teachings are limited to G28-5; Paulie implies that S2C6 can promote the proliferation of cancer cells; Hirano at best provides a general invitation to experiment in combining CD40 ligand with non-antagonistic CD40 antibodies for treating cancer; and de Boer teaches away from the presently claimed invention by teaching the humanization of CD40 antibodies that block the CD40-CD40 ligand interaction. Neither Riechmann or Greenwood remedy the deficiencies of Francisco, Paulie, Hirano or de Boer. Riechmann and Greenwood generally teach human constant domains and IgG isotypes, respectively, without any suggestions of molecules comprising the sequences of the S2C6 heavy chain CDRs or variable region (or closely related sequences) fused to a heterologous molecule. Accordingly, the rejection is improper and should be withdrawn.

Further, in making the argument that molecules comprising the sequences of heavy chain CDRs or heavy chain variable region of S2C6 and closely related sequences are obvious, the Examiner follows essentially the same obviousness analysis disallowed in *In re Deuel*, 51 F.3d 1552 (Fed. Cir. 1995). Specifically, as stated by the Federal Circuit, the existence of a general method of isolating molecules is essentially irrelevant to the question whether the specific molecules themselves would have been obvious, in the absence of other prior art that suggests the structures of the claimed molecules. *Deuel*, 51 F.3d at 1557-59. Thus even assuming, *arguendo*, that there were such a suggestion or motivation in the prior art "as a whole" to make molecules comprising the heavy chain CDRs or heavy chain variable region of S2C6, a finding of obviousness is improper without a specific suggestion of the claimed sequences, which none of the references cited by the Examiner provides.

Accordingly, Applicants submit that the rejection of claims 1-9, 21-25, 34, 38, 39, 42-44 and 47-91 under 35 U.S.C. § 103(a) as obvious over Francisco, Paulie, Hirano, de Boer, Riechmann and Greenwood has been obviated and should be withdrawn.

CONCLUSION

Applicants respectfully request that the above-made amendments and remarks be entered and made of record in the file history of the present application. The Examiner is invited to contact the undersigned with any questions concerning the foregoing.

Respectfully submitted,

Date: November 4, 2002

Adriane M. Antler 32,605
Adriane M. Antler (Reg. No.)

PENNIE & EDMONDS LLP
1155 Avenue of the Americas
New York, New York 10036-2711
(212) 790-9090

by: Muna Abu Shaar
Limited Recognition
Under 37 C.F.R § 10.9(b)
Copy of Certificate Enclosed